UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/700,338 | 11/14/2000 | Yoshiyuki Ueno | 1110-0279P | 3959 |

7590 07/27/2004

Birch Stewart Kolasch & Birch
PO Box 747
Falls Church, VA 22040-0747

| EXAMINER | |
|---|---|
| WINKLER, ULRIKE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/700,338 | UENO, YOSHIYUKI | |
| | Examiner | Art Unit | |
| | Ulrike Winkler | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8 and 10-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 10-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## REQUEST FOR CONTINUED EXAMINATION

The request filed on May 14, 2004 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/700,338 is acceptable and a RCE has been established. Claims 8 and 10-18 are pending and are currently under prosecution. An action on the RCE follows.

The Amendment filed March 15, 2004 in response to the Advisory Action of January 28, 2004 is acknowledged and has been entered with the entry of the RCE.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

### *Claim Rejections - 35 USC § 103*

The rejection of claims 8, 10-16 and newly added claims 17-18 under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997) in view of Harada et al. (Hepatology 1997, see IDS) and further in view of Shirakawa et al. (U.S. Pat. No. 6,114,507) **is maintained** for reasons of record.

The instant invention is drawn to a method of preventing and treating **hepatic cirrhosis** (biliary cirrhosis, primary biliary cirrhosis) **or bile duct disappearance syndrome** (caused by an immunological mechanism) (claims 8, 14-17). Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22), therefore, the same mechanism that are involved in primary biliary cirrhosis would be involved in bile duct disappearance syndrome. The method of treatment is achieved by administering a Fas antagonist to a patient. The Fas agonist is a substance that suppresses binding between Fas and Fas ligand (claim 10).

The agonist is Fas derivative, a competitive inhibitor comprising is the extracellular domain of Fas. The extracellular domain of Fas may be a truncated form or a chimeric protein between the extracellular domain of Fas and Fc immunoglobulin (claims 11, 12).

Applicant's arguments, in the response of November 17, 2003 and the reply filed May 14, 2004 are that there is a lack of predictability in the art regarding the expression of Fas/CD95 on liver epithelial cells. To support their argument Applicants' cite several references. Applicant's cite Leithauser et al. and Harada et al. as indicating that liver epithelia cells express Fas/CD95. While Applicant's cite Hiramatsu et al. as showing no Fas expression on normal cells or primary biliary cirrhosis. The reference, however, indicates a strong correlation for the detection of Fas antigen in hepeotcytes infected with Hepatitis C virus, but not in normal liver tissue. More expression of Fas antigen was found in liver tissue with inflammation than in tissue without it. (Hiramatsu et al. page 1357, column 1, lines 4-17). Finally Applicants cite Graham et al. as indicating that the there is no change in the Fas/CD95 staining in primary biliary cirrhosis (PBC). Fas antigen is found in the cytoplasm of hepatocytes and bile ducts. Fas antigen can be expressed in bile duct cells during the process of the damage to these cells by HCV infection (Hiramatsu et al. page 1358, column 1, paragraph 3). The important point of the Graham et al. reference is that the PBC cells do express the Fas/CD95, thereby, the reference does not contradict the teaching of the Harada et al. cited by the office in the prior 35 U.S.C. §103 rejection. Harada et al. correlates a strong expression of CD95 in the epithelial cells with the injured bile ducts of PBC (see Harada et al. abstract). However, all references indicate that Fas/CD95 is present in the inflamed tissues; this observation goes directly to the treatment prong of the invention as the claims are drawn to methods of treating or preventing disease. Applicants

further argue that the Office did not take into consideration all the prior cited references. When weighing the probative value of references those references that have a publication date closet to the date of invention provide the better indication of the state of the art at the time of the invention. As the art progresses the experimental procedures improve and detection methods also improve because the tools used for detection purposes improve. Therefore, the Office does not agree with Applicants assessment that the references indicate a lack of predictability regarding the presence of Fas/CD95 on liver cell epithelia.

Applicants acknowledge that both the Kondo et al. reference and the Shirakawa et al. reference cited by the Office in the 35 U.S.C. §103 rejection "may suggest or motivate the use of Fas antagonist for treating hepatitis, however, neither reference discloses a relationship between Fas antagonist and hepatic cirrhosis". It is well established in the art that chronic hepatitis leads to hepatic cirrhosis, therefore, a method that will prevent the inflammation and destruction of liver cells (hepatocytes) will prevent the occurrence of hepatic cirrhosis. The claims remain rejected as being unpatentable over Kondo et al. (Nature of Medicine, 1997) in view of Harada et al. (Hepatology 1997, see IDS) and further in view of Shirakawa et al. (U.S. Pat. No. 6,114,507).

Applicants' arguments are that the presence of Fas, per se, cannot be used as a general indicator of pathology. Applicants' arguments are that there are contradictory reports in the art regarding the expression of Fas/CD95 on normal vs. pathological tissue. Applicants in their arguments have cited several references in an attempt to show that there is unpredictability in the art regarding the presence of Fas/CD95 on liver epithelial cells. In evaluating all the references it is clear that 3 out of the 4 references cited by Applicants place the Fas/CD95 antigen at the surface of normal liver epithelial cells, while the 4$^{th}$ reference indicates that Fas/CD95 is

expressed only on the cells that have been infected with Hepatitis C virus. For the Office, the important point of the Graham et al. reference is that the PBC cells do express the Fas/CD95, thereby, the reference does not contradict the teaching of the Harada et al. cited by the office in the prior 35 U.S.C. §103 rejection. Harada et al. correlates a strong expression of CD95 in the epithelial cells with the injured bile ducts of PBC (see Harada et al. abstract).

Applicants base their argument that low level of expression would prevent apoptosis from being mediated through the CD95/Fas pathway. Applicants are arguing that the Fas pathway is not powerful, however, the applied art establish the contrary, where Fas is tied to disorders mediated by the Fas apoptosis pathway. The statement that something is unlikely to occur is opinion by the author and is based solely on the low level of expression of CD95/Fas on these cells. It must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964).

The same paragraph cited by Applicant's (Graham et al. page 556, 2nd column lines 8-12) continues to state that this mechanism (Fas apoptosis) has been invoked for a number of inflammatory disease of the liver, especially viral hepatitis and ligation of constitutive expressed Fas/CD95 on hepatocytes by antibodies results in rapid apoptosis. The reference indicates there is no change in the expression Fas/CD95 in primary biliary cirrhotic livers (note a change in the level of CD95/Fas is not claimed). However, the reference goes on to say that they have shown the presence of proteins involved in executing apoptosis in primary biliary epithelial cells which is consistent with previous reports of apoptosis of these cells (Graham et al page 556, 2nd column

lines last paragraph). The reference has not provided any teaching that would suggest that CD95/Fas are not present on the primary biliary epithelial cells. The rejection by the Office is based on establishing that CD95/Fas is present on the primary biliary epithelial cells. Based on what was known in the art at the time of the invention was filed the Fas molecule is a known powerful molecule involved in the induction the apoptosis death pathway. One of ordinary skill would have been motivated to prevent the crosslinking of CD95/Fas in order to prevent induction of the death pathway.

Kondo et al. teaches that administration of the soluble form Fas into HbsAg transgenic mice prevented CTL-induced liver disease. Fas ligand (FasL) is expressed in activated T cells and induces apoptosis in Fas-bearing cells. A cytotoxic T lymphocyte (CTL) clone specific for hepatitis B surface antigen (HbsAg) causes an acute liver disease in HBSAg transgenic mice (see figures 3 and 5). The reference teaches the treatment of an animal patient in two experimental hepatitis models with soluble Fas (a Fas derivative) in order to inhibit disease progression in the patient. The reference does not teach that Fas is expressed on liver cells in primary biliary cirrhosis.

Harada et al. teach that Fas is expressed on a broad range of human tissue, including biliary epithelial cells. The reference teaches that interlobular bile ducts of primary biliary cirrhosis frequently expressed CD95 (Fas) antigen in a cytoplasmic and membranous pattern, in addition a high intensity of CD95 ligand (Fas-ligand) positive mononuclear cells was found in the same pathology samples (see page 1404, column 1, paragraph 2). The findings demonstrate that biliary epithelial cells in primary biliary cirrhosis undergo apoptosis in response to the Fas/Fas ligand mediated cross linking, suggesting that apoptosis is involved in the progression of

bile duct injury and loss. The reference does teach using a Fas antagonist to treat the primary biliary cirrhosis.

Shirakawa et al. teach an antibody directed to Fas ligand (see claim 1) and a method of treating systemic or topical pathological conditions caused by the interaction of Fas ligand with Fas. The method comprises administering to a patient a therapeutically effective dose of an anti-Fas ligand antibody, which suppresses Fas ligand induced apoptosis (see claim 22). The reference does not expressly teach treating primary biliary cirrhosis.

The combination of references teaches utilizing a Fas antagonist for the prevention of Fas/Fas ligand interaction *in vivo* in an animal/patient. The references teach that Fas is present in the cells involved in primary biliary cirrhosis. Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22) therefore the same mechanism that are involved in primary biliary cirrhosis would be involved in bile duct disappearance syndrome. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat primary biliary cirrhosis by disrupting the Fas/Fas ligand interaction that leads to apoptosis of the cells involved in primary biliary cirrhosis as taught by Harada et al. One having ordinary skill in the art would have a high expectation of success in utilizing Fas antagonists for the purpose of treating bile duct disappearance syndrome and primary biliary cirrhosis in a patient using the antagonist and treatment methods taught by either Kondo et al. and Shirakawa et al. Therefore the instant invention is obvious Kondo et al. in view of Harada et al. and further in view of Shirakawa et al.

New Rejections in view of Amendments:

Claims 8, 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997) in view of Harada et al. (Hepatology 1997, see IDS) and Shirakawa et al. (U.S. Pat. No. 6,114,507) as evidenced by Galle et al. (Journal of Experimental Medicine, 1995), Dienes et al. (Virchows Archievs 1997) and Luo et al. (Journal of Viral Hepatitis, 1997).

The instant invention is drawn to a method of preventing **and** treating hepatic cirrhosis (biliary cirrhosis, primary biliary cirrhosis) **or** bile duct disappearance syndrome (caused by an immunological mechanism) (claims 8, 14-16). Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22). The method is achieved by administering a Fas antagonist to a patient. The Fas agonist is a substance that suppresses binding between Fas and Fas ligand (claim 10). The agonist is Fas derivative, a competitive inhibitor comprising is the extracellular domain of Fas. The extracellular domain of Fas may be a truncated form or a chimeric protein between the extracellular domain of Fas and Fc immunoglobulin (claims 11, 12).

Kondo et al. teaches that administration of the soluble form Fas into HbsAg transgenic mice prevented CTL-induced liver disease. Fas ligand (FasL) is expressed in activated T cells and induces apoptosis in Fas-bearing cells. A cytotoxic T lymphocyte (CTL) clone specific for hepatitis B surface antigen (HbsAg) causes an acute liver disease in HBSAg transgenic mice (see figures 3 and 5). The reference teaches the treatment of an animal patient in two experimental hepatitis models with soluble Fas (a Fas derivative) in order to inhibit disease progression in the

patient. The reference does not teach that Fas is expressed on liver cells in primary biliary cirrhosis.

Harada et al. teach that Fas is expressed on a broad range of human tissue, including biliary epithelial cells. The reference teaches that interlobular bile ducts of primary biliary cirrhosis frequently expressed CD95 (Fas) antigen in a cytoplasmic and membranous pattern, in addition a high intensity of CD95 ligand (Fas-ligand) positive mononuclear cells was found in the same pathology samples (see page 1404, column 1, paragraph 2). The findings demonstrate that biliary epithelial cells in primary biliary cirrhosis undergo apoptosis in response to the Fas/Fas ligand mediated cross linking, suggesting that apoptosis is involved in the progression of bile duct injury and loss. The reference does teach using a Fas antagonist to treat the primary biliary cirrhosis.

Shirakawa et al. teach an antibody directed to Fas ligand (see claim 1) and a method of treating systemic or topical pathological conditions caused by the interaction of Fas ligand with Fas. The method comprises administering to a patient a therapeutically effective dose of an anti-Fas ligand antibody, which suppresses Fas ligand induced apoptosis (see claim 22). The reference does not expressly teach treating primary biliary cirrhosis.

Galle et al. indicates that Fas/CD95 messenger RNA was absent in normal liver but was present in high levels in liver with ongoing liver damage, due to viral related hectic cirrhosis and acute hepatic failure. In patients with alcoholic liver damage CD95 ligand was expressed directly in the hepatocytes (see abstract). The reference demonstrates that anti Fas antibodies rapidly induce apoptotic cell death in primary human hepatocytes (see discussion and figure 2).

The results confirm the expression of Fas/CD95 in normal human liver at constitutive low expression levels (see discussion, page 1227, column 2, paragraph 2).

Diens et al. indicate that in primary biliary cirrhosis the bile duct epithelial cells mostly express CD58, CD80 and Fas/CD95 (see abstract). The reference investigated the expression of Fas/CD95 and found it to be present on the medium sized and interlobular bile ducts (see page 123, column 1, paragraph 4 and table 2).

Luo et al. indicate that during hepatitis B infection the expression of Fas is upregulated ib hepatocytes which render the hepatocytes more susceptible to FasL stimulation leading to apoptosis (see introduction). Fas expression is seen in inflamed liver tissue (see table1). The refence also teaches that the inflamed hepatocytes also express FasL suggestion an autocrine or paracine cell death mechanism.

The combination of references teaches utilizing a Fas antagonist for the prevention of Fas/Fas ligand interaction *in vivo* in an animal/patient. The references teach that Fas is present in the cells involved in primary biliary cirrhosis. Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22) therefore the same mechanism that are involved in primary biliary cirrhosis would be involved in bile duct disappearance syndrome. The additional references provide further evidence that Fas and FasL are upregulated in inflamed liver tissues. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat primary biliary cirrhosis by disrupting the Fas/Fas ligand interaction that leads to apoptosis of the cells involved in primary biliary cirrhosis as taught by Harada et al. One having ordinary skill in the art would have a high expectation of success in utilizing Fas antagonists for the purpose of treating bile duct disappearance syndrome

and primary biliary cirrhosis in a patient using the antagonist and treatment methods taught by either Kondo et al. and Shirakawa et al. Therefore the instant invention is obvious Kondo et al. in view of Harada et al. and Shirakawa et al. as evidenced by Galle et al., Dienes et al. and Luo et al.

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. JP9-124509-A (Seino et al.) May 13, 1997.

No claims allowed.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 7/26/04